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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/028,741
Filing Date: December 20, 2001
Appellant(s): KUROSAWA ET AL.

Steven L. Highlander
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 08/15/05 appealing from the Office action mailed 06/17/05.

(1) Real Party in Interest

A statement identifying the real party of interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Esmon et al., Thrombosis and Haemostasis (1999 August) 82(2):251-258

Kurosawa et al., (#C8) Blood (1998) 91:725-727

Hirsh et al., (#C6) Chest (1998 November) 114(5):445S-469S

Gu et al.,(#26) Blood (2000) 95(5):1687-1693

Guidici et al., (#C25) Haematologica (1999) 84:452-460

Kahn et al., J. Clin. Invest. (March 1999) 103(6) :879-887

Debeir et al., (1997) Eur. J. Pharm. 323:111-117

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Esmon et al. (Thrombosis and Haemostasis (1999 August) 82(2):251-258) and Kurosawa et al. (#C8, Blood (1998) 91:725-727) and in view of Hirsh et al. (#C6, Chest (1998 November) 114(5):445S-469S).

Esmon et al. teach a method of monitoring thrombin levels in patients undergoing anticoagulant therapy comprising the administration of hirudin, a specific thrombin inhibitor, by measuring circulating levels endothelial protein C receptor (EPCR), which receptors are necessarily soluble if circulating. Inhibition of thrombin by hirudin blocked increase in circulating EPCR (sentence bridging pages 254-255) in rats. Therefore, low levels of circulating EPCR corresponded to reduced levels of thrombin. Additionally, it was reported (p. 255, col. 2, third full sentence) that soluble EPCR (sEPCR)was present at high levels in the plasma of normal individuals and was increased several fold in patients with diseases associated with hypercoagulation (autoimmune disorders and septic shock, specifically systemic lupus erythematosus (see #C8, Kurosawa et al., Fig. 1)). It is concluded (p. 255, col. 2, first full paragraph) that "This [monitoring of plasma EPCR levels] could prove useful in monitoring the progression of cardiovascular disease or the effectiveness of therapeutic interventions in these [human] patients."

Kurosawa et al., referenced by Esmon above, teach detection of sEPCR by ELISA in human patient blood plasma (Fig. 1). Tests showed that in patients with diseases often complicated by thrombotic tendency and hypercoagulation, levels of sEPCR were significantly increased compared to normal control humans.

Hirsh et al. teach oral anticoagulant therapy for human patients with the anticoagulant Warfarin (*e.g.*, p. 446S, col. 1, second full sentence) and heparin (p. 463S, col. 2, second full paragraph). Also taught is the use of a vitamin K antagonist in anticoagulant therapy (p.445S, col. 2, middle of first full paragraph). Hirsh et al. also teach monitoring the effectiveness of anticoagulant therapy by measuring the prothrombin time (PT) as an international normalized ratio (INR, *e.g.*, Table 1 and section beginning at the bottom of p. 448S). Hirsh et al. points out that monitoring PT alone is not as reliable a measure of effectiveness of antithrombin therapy as the measure of both PT and INR (*e.g.*, p. 449S, col. 1, second to last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to monitor the effectiveness of anticoagulant therapy by measuring circulating sEPCR in human patients using the method of Esmon et al. and Kurosawa et al., because Esmon et al. teach that circulating sEPCR levels are decreased by administration of the anticoagulant hirudin and increased in hypercoagulation states and Kurosawa et al. teach that increased plasma sEPCR levels are associated with hypercoagulative states or risks. Also, the rodent experimentation of Esmon was conducted with the purpose of clinical application of the findings to humans. Therefore, the artisan of ordinary skill would have reasonably expected that the effects of an anticoagulant, including heparin or Warfarin taught by Hirsh et al., could have been adequately monitored by measuring circulating sEPCR levels. Further, since Hirsh et al. discussed the difficulties in using PT and INR for monitoring anticoagulation therapy effectiveness, one of ordinary skill in the art would have desired to use a more consistent measurement and one that involved testing a single thing (sEPCR) instead of multiple interacting things (PT and INR). Because vitamin K antagonists were known to be anticoagulants, it would have been obvious to include a vitamin K antagonist when thrombin levels or anticoagulation therapy were being monitored.

(10) Response to Argument

Appellants ague (p. 4 of Brief) that on the basis of the following passage from Esmon et al. at p. 255, it cannot be asserted that the reference adequately disclosed the use of sEPCR assays to monitor the effectiveness of anticoagulation therapy: "This [monitoring of plasma EPCR levels] could prove useful in monitoring the progression of cardiovascular disease or the effectiveness of therapeutic interventions in these [human] patients." This has been fully considered, but is not persuasive. The cited passage is only part of the teachings relied upon. As stated in the final Office action mailed 02/10/05 (first paragraph of p. 4):

> Further, Esmon et al. discuss mutations in the human thrombin gene in as a marker in some patients with myocardial infarction, who are 5 times more likely to have such a mutation than normal controls. Mutations in the thrombin gene can also lead to thrombosis in mice. "Taken together, these observation provide a firm clinical basis to conclude that the members of this pathway are critical to adequate negative regulation of the blood clotting system" (col. 2 of 252).

This teachings was not relied upon alone, but in combination with those of and Kurosawa et al. (#C8, Blood (1998) 91:725-727) and in view of Hirsh et al. (#C6, Chest (1998 November) 114(5):445S-469S) as discussed in the rejection repeated above.

Appellants argue (pages 4-5) that Gu et al. (Blood, 95(5):1687-1693, 2000) was designed as an *in vivo* model to study sEPCR generation and not sEPCR level changes in patients in response to anticoagulant therapy. Further, there are no human patients and no confirmation or testing of the theory that sEPCR levels may be linked to thrombin production in humans as suggested by the data. This has been fully considered, but is not persuasive. As stated in the final Office action (2/10/05, ¶ 2, p. 5), "Absent evidence to the contrary, mouse and human thrombin/coagulation systems are sufficiently similar for one to be used as a reasonable model for the other (see paragraph two above this). Fortunately, the art need not rely on the findings of Gu et al. alone, but has the teachings of others supporting the connection of sEPCR to thrombin and coagulation in humans and rodents. Absolute predictability is not required, but that the artisan of ordinary skill would reasonably expect the findings in the model of Gu et al. be applicable to the humans."

Appellants urge that the citation of Esmon et al. at p. 255, col. 2, in support of the teachings of Gu et al. (*supra)* from the advisory action mailed 6/17/05, does not suggest

anticoagulation therapy in humans can be monitored using the claimed methods. This has been fully considered, but is not persuasive. When the teachings of Esmon are taken in context and in light of the discussion in Esmon, it can be seen that the autoimmunde disorders and septic shock referred to Esmon are diseases/disorders associated with hypercoagulation (reference number 75 of Esmon et al., which is Kurosawa et al., see Fig. 1). Esmon et al. state in the third sentence of col. 2 on p. 255 that in **humans**, sEPCR levels were several fold higher in individuals with these diseases/disorders associated with hypercoagulation compared to sEPCR levels in plasma of normal individuals. Conversely, the skilled artisan would reasonably assume that if hypercoagulation in humans corresponds to relatively high levels of sEPCR, then anticoagulants would result in relatively lower levels of sEPCR. It is maintained that Esmon et al. does suggest that anticoagulation therapy in humans can be monitored by measuring circulating levels of sEPCR, *i.e.*, that found in plasma.

Appellants urge (p. 5 bottom) that "the need to conduct studies in humans is at the crux of the rejection, namely the lack of likelihood of success in practicing the claimed invention based only [on] animal studies." This has been fully considered, but is not persuasive. Lower levels of rat sEPCR resulted from anticoagulant treatment and corresponded to reduced levels of thrombin. However, as can be seen from the discussion in the immediately preceding paragraph, there is strong human evidence to corroborate the animal studies to support the Examiner's conclusion that the invention is obvious with a reasonable expectation of success supported by the prior art. The human findings discussed by Esmon et al. are the corollary of the findings in rat. Esmon continues on p. 255, col. 2, end of the first full paragraph, referring the findings in humans, "This [monitoring of sEPCR levels] could prove useful in monitoring the progression of cardiovascular disease or the effectiveness of therapeutic interventions in these [human] patients." The Esmon *et al.* reference itself suggests usefulness of monitoring sEPCR levels in humans and supports that suggestion with studies from rat **and** human.

Appellants cite *In re Vaeck* (Fed Cir. 1991) at the bottom of p. 5 to support the need for likelihood of successfully practicing the claimed invention based only on animal studies. The argument has been fully considered, but is not persuasive. *Vaeck* deals with producing different proteins in cyanobacteria. It does not deal with the argument at hand, that is the predictability of a rat model sEPCR assay for human use.

Appellants argue (paragraph bridging pages 5-6) that some prior art supports the use of animal models and some does not. The argument has been fully considered, but is not persuasive. As stated in the previous Office action (6/17/05, paragraph beginning bottom of p. 2), "This is correct and the applicability of an animal model to human patients is dependent on what is being modeled and analyzed. Applicability must be taken on a case by case basis. In the instant situation, the prior art supports use of the rat model for measurement of sEPCR for monitoring thrombin levels. It further should be noted that the claims are drawn to assaying not methods of treatment, which have additional considerations when evaluating the reliability of an animal model."

Appellants argue (first full paragraph of p. 6) that the Examiner simply dismissed Appellants' previous arguments relating to the use of rodent models as "not persuasive". Additionally, Appellants point out that binding of thrombin to its receptor is **distinct** from its clotting function, which is an acellular phenomenon. The argument has been fully considered, but is not persuasive. It can be seen from the discussion of Appellants' arguments in the previous Office actions (2/10/05, pages 4-6; 6/17/05, pages 2-4) by the Examiner that the arguments were not dismissed, but considered and responded to. While the research teaching correspondence of mutatations in the thrombin gene between mice and humans, which was previously discussed by the Examiner, does not deal with clotting, it does point to the similarity of mice and human in thrombin gene function, which is involved in clotting.

Appellants argue (middle of p. 6) that Guidici et al. (Haematologica, 84:452-460, 1999) did not report that humans can be protected from sepsis by antithrombin, only that a small subpopulation ***may*** benefit from such treatment. However, this subpopulation is a very particular group and not a generally representative sample of "patients with sepsis". Additionally, there was ***no*** difference in moratility of placebo or antithrombin beyond 30 days. Therefore, the results of Guidici et al. do not support recommendation of antithrombin therapy for treatment of sepsis. The argument has been fully considered, but is not persuasive. The Examiner's intent when discussing Guidici et al. was not to teach a method of treatment for sepsis by using anticoagulation therapy, but instead to show similarities of animal and human models in which anticoagulation treatment was used and the advantage of monitoring the success of anticoagulation therapy. The results discussed by Guidici et al. suggest that in septic shock

animal models in which sepsis was caused by *E. coli*, and in a subpopulation of humans with septic shock, anticoagulant therapy improved survival for a certain time period (see Office action mailed 6/17/05, middle of p. 4). Whether or not the therapy of Guidici et al. was successful, monitoring the success of the therapy was. Anticoagulation therapy is widely used for humans in need thereof.

Appellants argue (p. 7, top) that in the instant case, the artisan of ordinary skill cannot extrapolation from the animal studies of Esmon et al. to reasonably predict whether prior art rodent findings would be applicable to humans in order to render the present invention obvious. The argument has been fully considered, but is not persuasive. As stated in the final Office action (2/10/05, first paragraph of p. 4):

> [I]t is concluded (p. 255, col. 2, first full paragraph) by Esmon et al. that "This [monitoring of plasma EPCR levels] could prove useful in monitoring the progression of cardiovascular disease or the effectiveness of therapeutic interventions in these [human] patients." Further, Esmon et al. discuss mutations in the human thrombin gene in as a marker in some patients with myocardial infarction, who are 5 times more likely to have such a mutation than normal controls. Mutations in the thrombin gene can also lead to thrombosis in mice. "Taken together, these observation provide a firm clinical basis to conclude that the members of this pathway are critical to adequate negative regulation of the blood clotting system" (col. 2 of 252). Both the above conclusions support extending the rodent results to humans. Further, Giudici et al. (Haematologica, 1999, #C25 cited by Applicants) teaches that antithrombin infusion in animals receiving a lethal dose of *E. coli* provided a significant survival advantage. Simiarly, Giudici et al. also teaches that in a double-blind human study, administration of antithrombin conferred survival benefits to patients with severe sepsis and/or post-surgery complications (summarized in the second half of the Abstract).

It is maintained that the teachings of Esmon et al. combine data from rodents **and** humans, in addition to providing suggestions and motivations which would have provided the artisan of ordinary skill with a reasonable expectation of success. This conclusion is also supported by other prior art such as Guidici et al. (*supra*).

Appellants argue (paragraph bridging pages 7-8) that because humans and mice use different PAR receptors which are activated when thrombin cleaves it, causing signal transduction leading to platelet activation, then one cannot make conclusions for humans based

on findings in mice. The argument has been fully considered, but is not persuasive. As discussed in the previous Office action (6/17/05, middle of p. 3):

> It has been shown *e.g.*, Kahn et al., (1999) J. Clin. Invest., 1999) cited by Applicants on p. 7 of response, that humans use PAR-1 and PAR-4 receptors, while mice have no PAR-1 and use PAR-3 and PAR-4 instead. Even though there are different homologous receptors used in humans and mice, there is no expectation that the *intracellular* events are not at least on whole the same in rodents and humans. Further, the examiner has relied on teachings supporting this. Lower levels of rat sEPCR resulted from anticoagulant treatment and corresponded to reduced levels of thrombin (see Esmon et al., 1999). A corollary response was found in humans in that patients with a disease associated with hypercoagulation had higher levels of sEPCR (see previous Office action, p. 2, lines 19-24). Indeed, the prior art teachings do provide a reasonably expectation that as far as correlation of sEPCR levels with thrombin levels, rodents appear comparable to humans.

Further, the prior art (Debeir et al., (1997) Eur. J. Pharm. 323:111-117) showed that PAR-1 was present in rats and "...that rat astrocytes express PAR-1 receptors which are pharmacologically similar to those previously characterized in human platelets." (last sentence of abstract, see also Table 1). Debeir et al. shows the state of the prior art and is presented only as evidentiary information. While the pharmacology of rat and human PAR-1 is not identical, there is a similarity that cannot be ignored when comparing the two species. It is noted that Esmon et al., relied upon in the rejection, used rats and not mice in experiments. However, even if he had used the less similar mouse, there would still have been a reasonably expectation of correlation between rodents and humans as discussed in the previous Office action (see immediately above).

Appellants argue (p. 8) that there is no basis for the statement that, "Even though there are different homologous receptors used in humans and mice, there is no expectation that the *intracellular* events are not at least on whole the same in rodents and humans." The argument has been fully considered, but is not persuasive. The basis comes from the fact that homologous receptors generally function homologously, that is, similarly though not identically. It is more likely than not that if there is a family of receptors in one species that has a particular function (*e.g.*, activation by thrombin), then the homologous receptors in a different *mammalian* species would have the same activation, albeit not necessarily with identical pharmacokinetics. Fortunately, the artisan need not rely on the existence of a particular PAR alone to support or refute the similarity between rodents and humans in coagulation and sEPCR levels, but has a

number of teachings reviewed here to provide a reasonably expectation of the similarity in the connection of sEPCR to thrombin and coagulation in humans and rodents. Additionally, as is discussed in the preceding paragraph, the state of the art is illustrated by Debeir et al., where it was shown that there was homologous function of rat PAR-1 shared with human.

Appellants argue (p. 8) that Kurosawa et al. is not pertinent to the instant rejection or arguments "***since that paper did not deal with therapy!***" The argument has been fully considered, but is not persuasive. The instant claims are not drawn to therapy. They are drawn to a method of monitoring thrombin levels. Whether the thrombin levels are in a patient undergoing anticoagulation therapy, a patient in septic shock or with systemic lupus erythematosus, or a healthy human, the method of monitoring thrombin by measuring circulating levels of sEPCR is the same.

Appellants argue that because there is more genetic variability in the human population compared to mice because of the inbreeding of laboratory murine populations. As a result, conclusions drawn from mice (or rats) in complicated physiological responses seen in sepsis and clotting cannot readily be generalized to humans. The argument has been fully considered, but is not persuasive. As stated in the final Office action (2/10/05, p. 5, beginning line 18):

> Genetic variability in the human population was illustrated by the inventors in a paper published after the effective filing date of the instant application and discussed in the "***Prior Art***" section in the previous Office action as follows:
>
> > "...Stearns-Kurosawa et al., J. Thromb. Haemost. (2003 April) 1(4):855-856, teach that a bimodal distrubution of sEPCR is found in certain healthy populations (*e.g.*, those from Italy or France) and suggest that before using sEPCR as an indicator, gender and geographic location should be taken into account in determining what normal levels are. The latter reference suggests that that claimed invention may have inoperative embodiments, but this would be for a minority of the cases."
>
> Variability in the human population does not mean animal models cannot be used for what the artisan of ordinary skill would expect for the human norm, even though there might be exception. Animal models are not relied upon as exact replicas for human responses, but serve such that results obtained from an animal model can be extrapolated to humans. Animal models have and continue to serve as valuable models for many human diseases/conditions.

It is maintained the prior art supports the use of rodent models for monitoring sEPCR levels as shown by supporting data in humans as discussed in the rejection and above. For the reasons of

record and as discussed above that the artisan of ordinary skill would have accepted the rodent data for sEPCR as reasonably predictive of sEPCR behavior in humans.

In conclusion, the rejection is maintained because the claimed invention is obvious over the prior art relied upon, which provided a reasonably expectation of successfully monitoring sEPCR as claimed, as well as the suggestion and motivation to do so.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

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